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## EXTRACORPOREAL SHOCKWAVE THERAPY IN OSTEOPOROTIC OSTEOARTHRITIS OF THE KNEE IN RATS: AN EXPERIMENT IN ANIMALS

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**Purpose:** Osteoporosis (OP) can result in decreased bone mineral density, deterioration of bone quality and microarchitectural fracture of the subchondral bone. OP may increase the severity of cartilage damage in osteoarthritis (OA) knee, and the increases in cartilage damage correlate with bone loss and microarchitectural changes. These findings suggest an intimate relationship between OP and OA. Recent studies showed that extracorporeal shockwave therapy (ESWT) is chondroprotective in the initiation of knee OA and the regression of established OA of the knee in rats. However, no study reported an effective method in the prevention or reduction of osteoporotic osteoarthritis of the knee. The aim of the study was to investigate the effectiveness of ESWT in osteoporotic osteoarthritis of rat knee. We hypothesized that ESWT may be effective in the amelioration of osteoporotic osteoarthritis of the knee in rats.
**Methods:** Fifty-six female Sprague-Dawley (SD) rats were used in this experiment. The rats were divided into seven groups including sham, OA, OP, OA + OP, OA + ESWT, OP + ESWT, and OA + OP + ESWT groups. Group I was the sham group and received sham laparatomy without ovariectomy, and sham arthrotomy without anterior cruciate ligament transection (ACLT) and medial meniscectomy (MM). Group II was the OA group and received ACLT and MM and bilateral ovariectomies. Group III was the OP group and received bilateral ovariectomies. Group IV was OA+OP and received ACLT+MM and bilateral ovariectomies. Group V was OA+ESWT. Group VI was OP+ESWT and bilateral ovariectomes. Group VII was OA+OP+ESWT and received ACLT+MM, bilateral ovariectomies and ESWT. The evaluations included gross pathology, bone mineral density (BMD), micro-computed tomography (micro-CT) scan, bone-strength test, histopathological examination, and immunohistochemical analysis.
**Results:** On gross pathology, group OA + OP showed significantly larger areas of osteoarthritic changes than group OA and group OP, as compared with the sham group. BMD and bone strength significantly decreased in group OA, group OP, and group OA + OP relative to the sham group. ESWT significantly improved BMD and bone-strength changes. On micro-CT scan, the subchondral plate thickness was significantly decreased, and the bone porosity increased in group OA, group OP, and group OA + OP, and ESWT significantly improved the changes in subchondral-plate thickness and bone porosity. In histopathological examination, Mankin score and Safranin O score significantly increased in group OA and group OA + OP, but not in group OP relative to the sham group, and ESWT significantly improved the changes. In immunohistochemical analysis, Dickkopf-1 (DKK-1) significantly increased, but vessel endothelial growth factor (VEGF), proliferating cell nuclear antigen (PCNA), and bone morphogenetic protein 2 (BMP-2) decreased in group OA, group OP, and group OA + OP relative to the sham group, and ESWT significantly reversed these changes.
**Conclusions:** Osteoporosis increased the severity of cartilage damage in osteoarthritis of the knee. ESWT showed effectiveness in the amelioration of osteoporotic osteoarthritis of the knee in rats.

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## EFFECTS OF DIFFERENT DIETARY SATURATED FATTY ACID CONSUMPTION ON CARTILAGE HEALTH: EVIDENCE FROM PRECLINICAL RAT MODELS

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**Purpose:** The source, type and level of saturation of dietary fats may be critical factors underlying an inflammatory condition in articular joints and contribute to the development of osteoarthritis (OA).
Saturated fats are characterized as triglycerides with fatty acids that have no double bonds between carbon atoms. Western diet predominantly consist of fats rich in stearic acid, palmitic acid, myristic acid and lauric acid, all saturated fats. To date there are no studies that have investigated if any of these fatty acids can lead to articular cartilage damage in the joints. The goal of the present study is to evaluate the effects of different types of saturated diets on joint cartilage in a rat model.
**Methods:** To evaluate the chronic impact of a diet high in saturated fats on joint cartilage health,male wistar rats, weighing 330-340 g, were fed either a corn starch diet or a diet rich in simple sugars including fructose together with either lauric acid (C12), myristic acid (C14), palmitic acid (C16), stearic acid (C18) or beef tallow (mainly stearic and trans fatty acids). After 16 weeks, the knee-joints were assessed by micro-CT, histology, and immunohistochemistry for changes to articular cartilage, synovial membrane, and bone morphology. Serum cytokine concentrations were assessed with multiplex cytokine assays to determine levels of the inflammatory cytokines IL-1, IL-6 and TNF. The lipid profile, glucose levels, body weight and food consumption of the animals were recorded throughout the study period.
**Results:** This study showed that rats on high carbohydrate-, stearic acid-, or plamitic acid-rich diets had degenerative cartilage changes similar to that seen in OA cartilage. Suprisingly, animals that were fed lauric acid and myristic acid saturated fats had cartilage structures that were indistinguishable from corn starch fed controls, suggesting that the type of dietary fatty acids play a significant role in OA risk. As cartilage changes progressed, it was observed that diets supplemented with stearic acid and palmitic acid coincided with significantly increased glucose intolerance, abdominal obesity, hypertension and fatty liver, whereas rats fed lauric and myristic acid fats these effects lessened.
**Conclusions:** This study indicates that effect of saturated fats on OA risk depends on the type of fatty acids present in the food. Thus, reducing or modulating certain types of saturated fatty acids in the diet may contribute to prevent or slow the progression of OA.

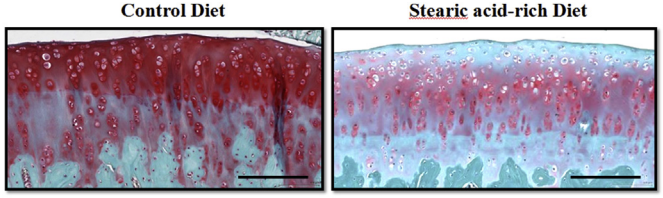


**Figure 1**: Rats that were fed with saturated fatty acid rich in stearic acid for 16 weeks showed altered cartilage morphology compared to control diet rat (n=6 rats).

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## THE INFLUENTIAL FACTORS FOR THE DEPRESSIVE STATE IN PATIENTS WITH KNEE OSTEOARTHRITIS

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**Purpose:** The symptoms of patients with knee osteoarthritis (OA) are often associated with a significant functional impairment, symptoms of inflammation, including pain, stiffness and loss of mobility, a disability of activities of daily living (ADL) and a diminished overall quality of life. The knee joint pain and the associated impairment of ADL in patients with knee OA are considered to affect the psychosocial status of patients. We previously reported that the pain severities of the patients with knee OA who were defined as a depressive state using a Zung self-rating depression scale (SDS) were significantly increased in comparison to those of the patients with knee OA who were not defined as a depressive state (OARSI 2014). However, it is still remained unclear what was the factor that affects the depressive state in patients with knee OA. In this study, we examined the factors those associated with a depressive state in patients with knee OA.
**Methods:** The two-hundred fifty subjects (mean age 70.7 years of age) who had visited our outpatient department with a chief complaint of knee joint pain between October 2009 and November 2012, showed the radiographic OA grade of Kellgren & Lawrence (K/L) grade 2 or greater and had no history of visiting hospitals for psychiatric disorder were enrolled in the present study. Patients showed either the K/L grade 2 (n=93), grade 3 (n=79) or grade 4 (n=78). The clinical manifestations were evaluated by using the Japanese Knee Osteoarthritis Measure

(JKOM) score (J Rheum 2005). The measure was proven to have sufficient reliability and validity by means of a statistical evaluation and comparison with other health-related scales such as the WOMAC and the SF-36. The Zung self-rating depression scale (SDS) was used to evaluate depression. When a patient showed SDS greater than 40, he/she was defined as a state of depression. Logistic regression analysis was conducted with statistics software SPSS (Ver. 21) using SDS scores as a dependent variable and clinical data (age, BMI, JKOM-pain and stiffness in knee, JKOM-condition in daily life, JKOM-general activities, JKOM-health conditions, radiographic knee OA severity [K/L grade 2 group and K/L grade 3 or 4 group]) as covariates. Each covariate was divided into two groups according to the median value.

**Results:** The ninety-three of 250 patients showed the K/L grade 2 group, while the remaining 157 patients showed the K/L grades 3 or 4. The mean SDS score of the patients in the present study was 39.6 points, and 50.8% (127 patients) of the patients were identified to be in a depressive state. No significant differences of the SDS scores of the patients with K/L grade 2 were observed in comparison to those of the patients with K/L grade 3 or 4. In logistic regression analyses using SDS as a dependent variable, the independent variables those had achieved a statistically significant regression coefficient were the following two factors: JKOM-condition in daily life scores [β=1.264, p=0.002, odds ratio (OR); 3.54 (95% CI; 1.57 to 7.99)] and JKOM-health condition scores [β=0.917, p=0.005, OR; 2.50 (95% CI; 1.32 to 4.76)].

**Conclusions:** Among the patients with knee OA, approximately half of the patients were defined as a depressive state. The radiographic OA severities of the patients were not associated with the depressive state, but the daily life conditions and the health conditions evaluated by the patient-oriented outcome measure were the independent significant influential factors for the severity of depressive state in patients with knee OA.

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## HISTOPATHOLOGICAL CLASSIFICATION AND SCORING OF OSTEOARTHRITIS AS A MULTI-TISSUE DISEASE

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**Purpose:** Osteoarthritis (OA) might be the end result of a variety of pathological processes in several joint tissues. Changes in articular cartilage, subchondral bone and synovium may each contribute to OA symptoms. Histopathological scoring systems for OA focus on articular cartilage. Although logically derived, they have been subjected to only limited validation and have reportedly poor ability to distinguish OA cases from healthy controls. Rasch analysis is a psychometric tool used to validate or improve outcome scales. We aimed to optimise the fit of the 4-item Mankin score to the Rasch model and extend this to develop a validated histopathological score that reflects OA as a multi-tissue disease.

**Methods:** Medial tibial plateaus and synovium were collected from 345 post-mortem (PM) and 143 total knee replacement (TKR) donations, and histological changes were graded. Osteophytes, a hallmark of OA, were visualised on the dissected knee for PM cases, or using radiographs in end-stage OA (TKR) cases. The presence of osteophytes or cases with end-stage OA (TKR) was used as reference standard for OA classification, and histopathological features were selected that displayed statistically significant associations with OA classification. The Mankin histological grading score was subjected to Rasch analysis and items were rescaled where appropriate, and supplemented with histological scores for subchondral bone marrow replacement by fibrovascular tissue and synovitis. Weightings for the 6 items were derived by principle components analysis (PCA). The resulting weighted 6-item score was compared with the original 4-item Mankin score using area under receiver operating characteristic curves (AUC). Multiple partitioning of the data was used to test reliability of the results.

**Results:** Cartilage integrity, chondrocyte appearance, proteoglycan loss, tidemark breaching, subchondral bone marrow replacement and synovitis were each significantly associated with TKR ($P \leq 0.006$) and with osteophytes ($P \leq 0.002$). Rasch analysis indicated misfit of the Mankin score to the Rasch model. Chondrocyte morphology scoring showed evidence of disordered thresholds, which was resolved by collapsing scores for chondrocyte hypercellularity and cloning. Person separation index was low (< 0.7). PCA indicated raw weightings which were transformed to produce a scale with a range of 0 to 10. The final score comprised of contributions of cartilage surface integrity (46%), proteoglycan depletion (20%), synovitis (16%), chondrocyte morphology (10%), subchondral bone marrow replacement (5%) and tidemark integrity (3%). The revised 6-item weighted score was better than the 4-item Mankin score for determining cases with end-stage OA (AUC; 0.85 and 0.75, respectively, P< 0.0001) or with osteophytes (AUC; 0.79 and 0.73, $P = 0.0001$).

**Conclusions:** Synovitis and subchondral marrow replacement by fibrovascular tissue are characteristics of knee OA, and incorporating histological scores for these features alongside chondropathy improved ability to distinguish OA from non-OA cases. Chondrocyte hypercellularity and cloning may not represent incremental OA severity, but rather be parallel processes in cartilage samples with similar chondropathy. Tidemark integrity is a feature of OA, but might contribute less to diagnostic classification than do chondropathy and synovitis. All histological scores tested displayed limitations as measurement tools, and better understanding of pathological processes in early disease is needed to inform further modifications that might improve targeting across the range of OA, including non-TKR populations.

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## BASELINE MAGNETIC RESONANCE IMAGING CARTILAGE T2 RELAXATION TIME MEASUREMENTS AS PREDICTORS OF TOTAL KNEE ARTHROPLASTY IN AFRICAN-AMERICANS – DATA FROM THE OSTEOARTHRITIS INITIATIVE

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**Purpose:** Total knee arthroplasty (TKA) represents a prevalent outcome for end-stage knee osteoarthritis (OA), but the procedure is costly and postoperative complications are common. We currently lack reliable prognostic markers that can be used at early stages of OA to predict the eventual need for TKA later on. A predictive biomarker of this nature could also be helpful to physicians and patients in their treatment planning. Thus, the aim of this study was to determine whether baseline cartilage T2 relaxation time obtained with 3 Tesla magnetic resonance imaging (MRI) can be used as a predictive biomarker for TKA 4 to 7 years later.

**Methods:** An observational nested case-control study was performed using data from the Osteoarthritis Initiative (OAI), a longitudinal multicenter study including 4796 subjects with or at risk of knee OA, with the exception of a small control group of subjects without OA risk factors. Subjects who sustained a right knee TKA 4 to 7 years following enrollment in the OAI study were identified as cases (n=81). Subjects without total knee arthroplasty but with radiographic knee OA were identified as controls (n=228). Subjects were frequency-matched using a 1:3 ratio of cases to controls according to the following parameters: baseline Kellgren-Lawrence grade (0-3), age (45-79 years), gender, BMI, and race (Caucasian-Americans: n= 70 cases, 204 controls; African-Americans: n= 8 cases, 22 controls). 3 Tesla magnetic resonance images were obtained in the right knee of each patient at the enrollment visit. Knee cartilage was segmented semi-automatically in a sagittal T2 map 2-D Multi-Slice Multi-Echo (MSME) spin-echo sequence. Mean cartilage T2 relaxation time values were quantified in 5 cartilage compartments: lateral femur (LF), lateral tibia (LT), medial femur (MF), medial tibia (MT), and patella (PAT). A global T2 value (GLO) per whole joint was obtained by calculating the mean of the T2 values per compartment. A conditional logistics regression model was run using STATA version 12 software (StataCorp LP, College Station, TX). Odds ratios were calculated per standard deviation (SD) change in T2.

**Results:** Although no associations were found between baseline T2 values and the occurrence of TKA in the entire cohort, stratification by race yielded significant associations. In the African-American cohort, a one SD rise in global baseline mean T2 value was significantly associated with an approximate 70% increase in the risk of undergoing TKA 4 to 7 years later (GLO: OR=1.74, p=0.04). Specifically, a one SD rise in lateral